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ON THE QUESTION OF THE MECHANISM OF IMPULSE TRANSMISSION FROM NERVE TO MUSCLE

«К вопросу о механизме перехода возбуждения с нерва на мышцу»

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From the point of view of the humoral concept, one of the most essential conditions for the passage of stimuli across the neuromuscular synapse is the sensitivity of the muscular fibers to a mediator. It is perfectly clear that if under certain influences the muscle fibers lose their ability to be excited by the mediator, then this must inevitably lead to the stoppage of stimulus-transfer across the neuromuscular junction.

The experimental verification of this hypothesis was first carried out by Bacq and his associates on the smooth muscle (in the third period of growth) of the cat. It was believed that the mediator in the transmission of the nerve impulse from the sympathetic post-ganglionic nerve fibers to this muscle was adrenaline. Bacq showed that under normal conditions adrenaline evokes practically the same contraction of this muscle as stimulation of the sympathetic nerve. Yet after the poisoning of this muscle with 933F the muscle ceases to react to adrenaline; nevertheless the same muscle will contract in response to a nerve impulse coming to it along the nerve fibers.

The fact that a contraction of the muscle is obtained in response to the nerve impulse after the humoral mechanism of transmission is inhibited with 933F shows that the transmission of excitation from the post-ganglionic sympathetic fibers to the smooth muscle takes place not only by humoral means by the intermediary of adrenaline, but also in some other way, apparently through action currents.

Subsequently, using this technique of inhibiting the humoral mechanism of nerve-impulse transmission, Bacq and Meunier on the one hand and Bacq and Bovet on the other succeeded in making clear the significance of both the humoral factor and of action currents in the mechanism of nerve transmission.

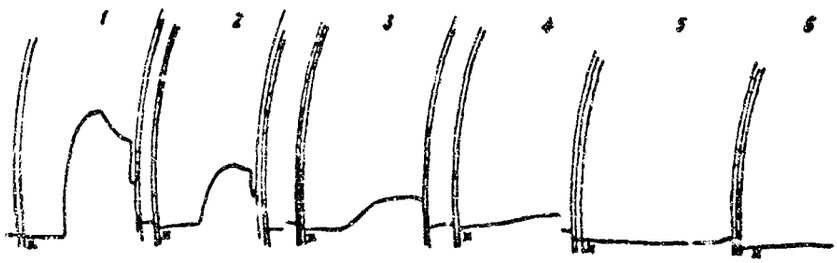
It appeared to us to be of interest to apply this device of blocking the humoral mechanism of transmission to the study of the passage of excitation from the motor nerve to skeletal muscle. Since in the case of skeletal muscle the mediator is believed to be acetylcholine, our task involved rendering the fibers of skeletal muscle insensitive to impulses coming to them along the nerve.

Beritov has shown that if acetylcholine acts repeatedly on skeletal muscle, it may, after a few minutes, fail to cause a contraction of the muscle. Investigating this phenomenon in more detail, we established that if we inject an acetylcholine solution (1:20,000) in small quantities (0.25 ~ 0.5 cm^3) several times in succession into the artery of the muscle, with intervals of 5 minutes between these injections, the intensity of the muscular contraction in response to each successive injection becomes less and less: finally it ceases altogether to respond with a contraction to the injection of acetylcholine. Thus the substance which will cause a loss of sensitivity of skeletal muscle to acetylcholine turns out to be acetylcholine itself.

It seems to be of interest to ascertain how the reaction of the muscle fibers to the nerve impulse changes after the muscle fibers have been rendered insensitive to acetylcholine.

PROCEDURE

The tests were carried out on neuromuscular preparations (*ischiadicus - gastrocnemius*) from the frog (*Rana ridibunda*). The muscle was perfused with Ringer's solution by way of a canula inserted in the ischiadic artery and connected through a three-way cock to two Mariotte bottles. Through the same canula, acetylcholine solution could be fed into the artery of the muscle. The nerve of the preparation was placed in a small moist chamber, where electrodes from the secondary winding of an ordinary variable-coupled induction coil were brought into contact with it. Recording of the muscular contractions was carried out on the smoked surface of the slowly rotating drum of an Engelman direct-acting myograph, with a 5 g load on the muscle.



Myogram of m. gastrocnemius of frog in response to separate indirect stimuli and in response to acetylcholine.

RESULTS

Shown in the figure are myograms illustrating the results of one of the tests. At 1 we registered, at the start of the test, two separate maximal contractions of the muscle in response to indirect excitation. The height of these contractions is a measure of the reaction of the muscle fibers to the nerve impulse. After this, 0.4 cm^3 of a 1:20,000 acetylcholine solution was injected into the muscle artery, over a period of minutes. As may be seen from the myogram, the response to the acetylcholine was a strong contraction of the muscle, reaching a height of 70% of that of a separate maximal contraction.

After 4 minutes, with the muscle now in a relaxed condition, we again subjected it to two separate maximal stimulations and then injected 0.4 cm^3 of the 1:20,000 acetylcholine solution (myogram 2). Comparison of myograms 1 and 2 shows that the height of separate muscular contractions evoked by indirect excitation is in both cases the same, while the height of the muscular contraction in response to the injection of acetylcholine is in the second case less than in the first case.

At the end of 5 minutes, when the muscle had relaxed from the second injection of acetylcholine, it was subjected to three separate maximal stimulations and again injected with 0.4 cm^3 of acetylcholine. As will be seen from myogram 3, the contraction and response to the injection of acetylcholine has become still less.

In myogram 4, recorded five minutes after myogram 3, the contraction of the muscle in response to the acetylcholine injection is quite insignificant. Upon the next injection, the muscle fails completely to react to acetylcholine at a concentration of 1:20,000 (myogram 5).

Myogram 6 illustrates the reaction of the same muscle to the injection of acetylcholine diluted 1:10,000. As will be seen from the myogram, acetylcholine at this concentration likewise fails to produce a contraction.

The results of the experiments show that the effect of repeatedly subjecting the muscle to the action of acetylcholine was that the latter lost its power to stimulate the muscle fibers. Yet the muscle reacted to indirect stimulation with contractions of almost the same strength as at the beginning of the test. The results of this experiment are essentially similar to Bacq's results, obtained upon the smooth muscle (third stage of growth) of the cat, with 933F intoxication: the muscle fibers, insensitive to the action of the mediator, react normally to the nerve impulse.

In a neuromuscular preparation of the skeletal muscle of the frog, the reverse of this phenomenon may easily be obtained: that is, the muscle subjected to a certain influence ceases to respond to the nerve impulses but reacts normally to acetylcholine.

Of particular interest from the point of view of the humoral theory is the inhibition of the nerve impulse transfer at the myoneural junction caused by an increased amount of potassium ions in the Ringer solution. As Yudenich's researches have shown, Ringer's solution with its content of potassium chloride increased to 0.05 ~ 0.06%, when perfused through the blood vessels of skeletal muscle, will cause the blocking of the impulse at the myoneural junction and the loss of the indirect excitability of the muscle.

We have carried out a series of tests in which we investigated the sensitivity of the skeletal muscles to acetylcholine subsequent to their loss of indirect excitability through the effect of perfusion with Ringer solution with an excess of potassium ions.

These tests showed that the sensitivity of such muscles to acetylcholine is not only not lower than that of normal muscles, but is even somewhat higher. Muscles poisoned by Ringer's solution with an excess of potassium ions (0.06%) react to a weaker concentration of acetylcholine than normal muscles, and in response to the acetylcholine injection they give a greater contraction.

From the point of view of the humoral theory, the blocking of the impulse at the myoneural junction may be explained either by there being an insufficient quantity of acetylcholine released at the nerve endings in response to the nerve impulse, or by the muscle fibers having lost their ability to react to acetylcholine. As has been shown by the researches of Beznack, Brown, Cowan and Feldberg, potassium ions not only do not inhibit the release of acetylcholine, but on the contrary they facilitate the liberation of acetylcholine by the nerve endings. Thus when skeletal muscle is poisoned by Ringer's solution with an excess of potassium ions, the nerve endings do release acetylcholine in response to the nerve impulse; the muscle fibers do react to acetylcholine; nonetheless the muscle does not react to the nerve impulse.

Our tests show that between the indirect excitability of the muscle, that is, between the ability of the muscle fibers to respond to the nerve impulse, and their sensitivity to acetylcholine, there is no direct relation. Muscle fibers may lose their ability to be excited by acetylcholine and yet at the same time show a good reaction to the nerve impulse. On the other hand, there may be a well-expressed sensitivity of the muscle fibers to acetylcholine without the nerve impulse always being able to cause them to contract.

All these results are difficult to reconcile with the theory that acetylcholine is the transmitter of excitation from the motor nerve to the skeletal muscle.